

*Children's Cancer Research Foundation, Inc.*

35 Binney Street, Boston, Massachusetts 02115

734-6000

Sidney Farber, M.D.  
Director of Research

July 20, 1971

Dr. Matthew Meselson  
Biological Laboratories  
Harvard University  
16 Divinity Street  
Cambridge, Massachusetts

JUL 22 1971

Dear Matt:

I am enclosing my statement which I just sent off to the EPA. Thanks for your much appreciated comments.

I heard this morning from Mr. Dominick, an assistant to Mr. Ruckelshaus, who was most cordial and expressed great interest of EPA to listen to other viewpoints on this matter. For these reasons, I would like to suggest that it might be useful if you would consider writing Mr. Ruckelshaus and expressing your views. Mr. Dominick also told me that in future, EPA would release such reports well in advance of the decision-making process. This is a useful step forward.

Additionally, I am enclosing a note from Bob Mann in New Zealand - can you possibly help him with a supply of dioxin?

With best wishes,



Samuel S. Epstein, M.D.  
Chief, Laboratories of Environmental  
Toxicology and Carcinogenesis

SSE/sa

Enclosure

Biochemistry Dept  
University of Auckland  
P.O. Auckland  
NEW ZEALAND

14 July 71

Dr S S Epstein  
Children's Cancer Research Fdn.  
35 Binney St  
Boston, Mass 02115, USA

Dear Sam,

Thanks very much for the latest batch of information on 2,4,5-T. Our govt Agricultural Chemicals Board is proud of its copy of the PSAC report, but thanksto you I'm able to handle their misinterpretations from it.

The head of our Paediatrics Dept and I went on TV and told the truth. It caused a great deal of interest within a radius of 100 miles which will we hope justify another, fuller coverage soon.

My central point was that farmhouses have in fact been sprayed from the air (by accident), and this could happen again. Here we use at least 4 lb/acre 2,4,5-T on gorse and blackberry; in one area near our city 17-20 lb/acre has been used on gorse: at the minimum, a farmhouse roof, approx. 1/20 acre, will collect 90 g 2,4,5-T; and on the makers' own claims, that's about 90 microg of "dioxin". But using the minimum teratogenic dose to hamsters, 0.02  $\mu\text{g}/\text{kg}$  (PSAC report p.52), and the WHO safety factor of 1/2000 to allow for the possibility that humans are more sensitive than hamsters, the likely dangerous dose to a woman is down in the region of 0.001  $\mu\text{g}$  dioxin. Many farmers here drink the water off their roofs. So in an accidental spraying such as has occurred with 2,4-D at least, the farmhouse water tank may well collect FIVE ORDERS OF MAGNITUDE more than the likely dangerous dose with respect to teratogenicity. (It is also, by the way, a couple of  $\text{LD}_{50}$ 's for an adult, using the guinea-pig  $\text{LD}_{50}$  of 0.6  $\mu\text{g}/\text{kg}$ .)

My next move is to analyse, by the GLC method published in the Hart report, samples of all the forms of 2,4,5-T sold in NZ. I have the equipment and student to do this. What I don't have is an authentic sample of the tetrachlorodioxin to calibrate the assays. I wrote to Dr Verrett some months ago asking for a sample but she has not replied.

Could you please arrange for a sample to be sent to me, by air? We have the govt here on the run and are keen to follow on.

Thanks again for your help so far.

Ⓟ  
Bob Mann

STATEMENT OF DR. SAMUEL S. EPSTEIN ON THE REPORT OF THE ADVISORY COMMITTEE ON  
2,4,5-T TO THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY

A. BACKGROUND TO REPORT

1. The original experimental data on the teratogenicity and fetotoxicity of the herbicide 2,4,5-T were obtained by Bionetics Research Laboratories, under contract to the National Cancer Institute, in July of 1966, and these experiments were amplified and completed by August 1968; these findings were, however, not publicly released until October 1969. Low doses of 2,4,5-T and some of its esters produced birth defects in mice and rats, and in rats "no effect" levels were not reached at even the lowest dose tested, 4.6 mg/kg.

2. On the basis of a detailed evaluation of the above data, the Teratogenicity Panel of Secretary Finch's Commission on Pesticides and Their Relationship to Environmental Health, HEW, December 1969 *unanimously* recommended. "The use of currently registered pesticides to which humans are exposed and which are found to be teratogenic by suitable test procedures in one or more mammalian species should be *immediately* restricted to prevent human exposure. Such pesticides in current use, include . . . . . 2,4,5-T".

3. The belated discovery of high concentrations of a tetradoxin contaminant, *ca.* 27 ppm, in the sample of 2,4,5-T tested by Bionetics Laboratories suggested the possibility that the reported teratogenic and toxic effects could in part be due to the contaminant rather than to the herbicide *per se*. It was also suggested that formulations with lower concentrations of the dioxin contaminant posed no potential teratogenic hazards.

4. In testimony on April 15, 1970 before Senator Philip Hart, Chairman of the Subcommittee on Energy, Natural Resources and the Environment, of the committee on Commerce, I emphasized the following:

a. Relatively pure samples of 2,4,5-T, with tetradoxin concentrations  $<1$  ppm, were teratogenic in 3 mammalian species--rats, mice, and hamsters, quite apart from similar effects in chicken eggs.

b. The production of a 39% incidence of congenital anomalies, including cystic kidneys, by administration of 4.6 mg/kg of the 2,4,5-T formulation tested by Bionetics Laboratories could not in all likelihood be due to its contamination with the dioxin, as equivalent concentrations of dioxins, ca. 0.125  $\mu$ g/kg, or even higher concentrations failed to produce a high incidence of cystic kidneys.

c. Apart from the tetradoxin isomer, there are approximately 60 other chloro- dioxin isomers, some of which could also be present in commercial 2,4,5-T formulations.

d. Available data on the tetradoxin indicated its extreme heat stability. Additionally, feeding *chicken edema factor* diets containing dioxins produced cumulative toxicity in monkeys, and storage of hexa-, hepta-, and octadioxin isomers has been reported in tissues of chickens and rats fed *chicken edema factor* diets. These and other data suggested the possibility of food chain transmission and accumulations of various dioxin isomers. For these reasons, even concentrations of tetradoxin  $<1$  ppm represented serious potential hazards. Cumulative toxicity apart, tetradoxin is one of the most potent known acute chemical toxins; the acute oral  $LD_{50}$  dose of tetradoxin in guinea pigs is ca. 0.6 ppb and the fetotoxic dose is less than 0.125 ppb.

e. Apart from any dioxin present in 2,4,5-T formulations, its approximate 5% content of polychlorophenols represented major additional potential sources of dioxin following combustion.

f. No data were available on effects of 2,4,5-T by inhalation,

although phenoxy herbicides have been detected in air at a distance from spraying operations; additionally no data existed on the carcinogenicity or mutagenicity of tetradoxins, quite apart from other dioxins.

4. On April 20, 1970, the Surgeon General announced the suspension of the use of 2,4,5-T over water, around homes and on food crops to minimize the risk to pregnant women. The Department of Defense also announced restrictions in military use over Vietnam, although it appears that such restrictions were not enforced till several months later.

5. Under Section 4C of the Federal Insecticide, Fungicide, and Rodenticide Act of 1947, 2 manufacturers of 2,4,5-T, Dow Chemical Co. and Hercules, Inc., in May of 1970, petitioned for an Advisory Committee to review the need for the imposed restrictions on 2,4,5-T.

6. The National Academy of Sciences were requested to supply a roster of individuals, from whom an Advisory Committee was then appointed by the Secretary of Agriculture. This Committee first met on February 1 and 2 of 1971.

7. At public hearings on May 13, 1971, before the Pesticide Board of the Commonwealth of Massachusetts, following the imposition of an emergency ban on aerial applications and other uses of 2,4,5-T, representatives of the National Agricultural Chemicals Association and of Dow Chemical Co., both referred to the report of the Advisory Committee as a National Academy of Sciences (NAS) Committee. In subsequent correspondence with Dr. Handler, President of the NAS, he clearly corrected this misstatement, "This committee is not a committee of the National Academy of Sciences or the Natural Research Council, and its advice is in no way subject to our usual review procedures". A representative of the National Agricultural Chemicals Association subsequently admitted to the use of "loose" terminology in misrepresenting the Advisory Committee as a National Academy of Sciences Committee.

8. The report of the Advisory Committee was submitted to EPA on May 7, 1971. Although the report of the Advisory Committee has still not yet been publicly released, a detailed critique of its contents and a discussion of its discrepancies and omissions was published in NATURE June 25, 1971 by their Washington correspondent.

B. RECOMMENDATIONS OF THE REPORT

The following recommendations were passed by 9 of the 10 members of the Advisory Committee:

1. All restrictions on the use of 2,4,5-T should be removed.
2. Residues of 2,4,5-T must be  $<0.1$  ppm in food and in drinking water.
3. Existing stocks of 2,4,5-T with 0.5 ppm of tetradoxin may be used, except domestically.
4. Future formulation of 2,4,5-T must contain  $<0.1$  ppm of tetradoxin.
5. Household formulations of 2,4,5-T must carry a label warning of dangers to pregnant women.
6. Further research should be undertaken to study whether dioxins accumulate in the soil and food chains.

One dissenting member issued his own strongly worded minority report, which is not only highly critical of the majority report, but which argues that most existing restrictions on 2,4,5-T be maintained.

C. CRITIQUE OF THE ADVISORY COMMITTEE REPORT BY THE COMMITTEE FOR ENVIRONMENTAL INFORMATION

1. The report was not intended to be made public prior to its use as the basis for a policy decision by the Environmental Protection Agency. Although the report deals with issues of critical concern to the scientific and general communities, no opportunity for independent scientific review of the report has been made formally available. We fully concur with Dr. John Edsall's criticisms on the attempts at secrecy prior to the decision making process.

2. An attached critique of the report prepared by the Committee for Environmental Information has been supported by:

a. Dr. Barry Commoner, Chairman, Scientists Institute for Public Information, and Director of the Center for the Biology of Natural Systems, Washington University.

b. Dr. John T. Edsall, Professor of Biological Chemistry, Harvard University.

c. Dr. Samuel S. Epstein, Chief, Laboratories of Environmental Toxicology and Carcinogenesis, Children's Cancer Research Foundation, and Harvard Medical School, and newly appointed Swetland Professor of Environmental Health and Human Ecology at Case Western Reserve University.

d. Dr. Arthur Galston, Professor Biology, Yale University.

e. Dr. Michael Prival, Department of Biology, Massachusetts Institute of Technology, and Chairman, Subcommittee on Pesticides, Union of Concerned Scientists.

f. Dr. Jeremy Stone, Director, Federation of American Scientists.

g. Mr. Harrison Wellford, Associate, Center for the Study of Responsive Law, Washington, D. C.

h. Additionally, general letters of support have been received from Dr. Matthew Meselson of the Department of Biology, Harvard University and Chairman of the AAAS Herbicide Assessment Commission, and from Dr. James Crow, Chairman of

the Department of Genetics, University of Wisconsin.

D. FURTHER CRITIQUE OF THE ADVISORY COMMITTEE REPORT

1. The Advisory Committee conferred with 22 outside persons including 6 representatives of the 2 petitioners. With the exception of a legal representative from the Center for the Study of Responsive Law, the committee conferred with no scientists, such as Dr. A. Galston, Dr. M. Meselson, Dr. J. Verrett, who had expressed concern on the teratogenic hazards of 2,4,5-T and who were critical of removal of restrictions on its use, and with no representatives of environmental or ecological groups; the committee, in fact, refused to accept evidence from the Environmental Defense Fund. The decision to exclude evidence from the environmentalists was apparently taken unilaterally by the Chairman of the Committee, although the majority of the Committee are alleged to have expressed a contrary opinion at the first meeting.

2. The Advisory Committee, with one dissenting member, takes the view that, in spite of many admittedly unanswered questions, the public may be exposed first and the experiments performed later. This is in direct contradiction to the philosophy and statements recently expressed by Mr. William Ruckelshaus, Administrator of the Environmental Protection Agency, in his speech of March 9, 1971 before the Society of Toxicology:

"For the past several decades we have been heedlessly introducing into our environment a multitude of chemical, biological, and physical contaminants with very little idea of what we are doing to ourselves or other life forms with whom we share this planet. The time has come when this has to stop. . . . There's the recent discovery of gross mercury contamination, a good example of what happens when we dump first and research afterwards. . . . Therefore, as we seek more and better data in the toxicological field, it is absolutely essential that we act on the knowledge we already have or face the possibility of irreversible

environmental  
/harm and even tragic damage to the lives and health of our own or future generations".

3. In the Committee's brief discussion of the Bionetics studies, no reference is made to the rat data, where dose response relationships were established and no effect levels were not reached at the lowest dose tested, 4.6 mg/kg.

4. Much of the report is based on unpublished data and reports which have not been subject to customary independent scientific review, and whose validity must therefore be open to question.

5. Several recent experiments demonstrating the teratogenicity of "pure" 2,4,5-T have been discounted by the Advisory Committee on the grounds that dosages used, *ca.* 100 mg/kg, were too high. Yet, there are other studies that show definite teratogenic and fetotoxic effects at lower dose levels. Additionally, in the experiments conducted by Dow Chemical Co., 2,4,5-T at concentrations of 24 mg/kg, with *ca.* 0.5 ppm dioxin contaminants, produced an approximately 7-fold increase in incidence of sternebral ossification defects in rats as compared with controls. It should also be pointed out that much of the data reviewed by the Committee were based on tests at relatively high dose levels, and that there is a serious inadequacy of data at the purportedly more critical low dose levels.

6. As the dissenting Committee member expressed it, "The report presumes to lecture the scientific community on the wisdom of instituting a 'permissible residue' of substances thought to be teratogenic". The claims by the committee that there are threshold levels for the teratogenic effects of 2,4,5-T and dioxins are completely unsubstantiated. Again, with the exception of the dissenting member, the Committee ignores the insensitivity of teratogenicity testing in animals, as a function of small test sample size compared with the millions of humans at presumptive risk. To illustrate this, assume that an environmental contaminant produces birth defects, or other adverse effects such as cancer, in 1/10,000 humans

which are exposed to it; assume further that the sensitivity of humans and rodents are similar, the groups of 10,000 mice or 10,000 rats minimally would be required for the demonstration of one adverse effect if tested at levels of human exposure; for statistical significance, perhaps groups of 30,000 rodents would be required. In fact, test groups are usually based on less than 50 animals. In an attempt to reduce the gross insensitivity of such toxicological procedures, it is customary and accepted practice to test at levels higher than those to which humans are exposed. It becomes a *reductio ad absurdum* to discount the validity of such high dose data, when low dose data statistically cannot possibly demonstrate effects.

7. Apart from its unwarranted assumptions on the existence of threshold effects for the teratogenicity of 2,4,5-T, the Committee ignores the real possibility that humans may be more sensitive to the teratogenic effects of 2,4,5-T than rodents. Indeed this is the case with thalidomide, the minimal teratogenic dose of which in humans is *ca.* 0.5 mg/kg/day; the pregnant human female is 60 times more sensitive to thalidomide than are mice, 100 times more sensitive than rats, 200 times more sensitive than dogs, and 700 times more sensitive than hamsters. So that, even if pure 2,4,5-T was teratogenic to rodents only at doses as high as *ca.* 100 mg/kg--and there is little evidence that this, in fact, is the case--, this would not preclude the possibility of serious potential human teratogenic hazards.

8. The Chairman of the Advisory Committee, a well-known teratologist, performed some rather unusual experiments with small numbers of animals and no concurrent controls, which in fact, showed fetotoxic trends at the lowest dose tested, 20 mg/kg; these effects are unaccountably ignored in the report. Commenting on these experiments, another committee member is alleged to have stated that the Chairman "Would never have published these data". However, data that do not merit publication should clearly not be cited in support of decision making processes.

9. The Committee fails to point out a serious error in a Hercules Corporation-

sponsored study, which was reported to it, where no effects were claimed with pure 2,4,5-T at 113 mg/kg doses in mice, when in fact the dosage mistakenly used was 10 mg/kg. A subsequent repeat test at correct dosage levels confirmed teratogenic effects, *i.e.*, an 11% incidence of cleft palates in mice with a Dow formulation, and a 1% incidence with a Hercules formulation; the Advisory Committee made no comment on this important and striking discrepancy. When challenged on this, the Committee Chairman is alleged to have charitably indicated that he would rather not air a mistake: "They made a mistake--so do we all".

10. The Committee concludes that 2,4,5-T will rapidly break down in the environment, and ignores the possibility that certain bound forms in plants may not be detected by currently used techniques, without initial acid extraction.

11. The Committee's discussion on dioxins suffers from certain apparent errors and unsubstantiated assumptions. These include the following:

a. The Committee states that further research should be undertaken to study whether dioxin accumulates in the soil and food chains. Paradoxically, the Committee nevertheless concurs that it is "virtually impossible" for anyone to be exposed to toxic doses with currently produced 2,4,5-T. This conclusion is based on the unsubstantiated belief that dioxin does not accumulate in the air, water, plants, or in the food chain; it is, however, admitted that the tetradoxin is highly persistent and can persist for over a year in soil. The Committee's confidence is also based on the belief that dioxins are poorly soluble in oils, and thus would not accumulate in body fat. This is directly contradicted by available information on dioxins, which are causally responsible for chick-edema disease and which are found in certain batches of cotton seed oil; feeding of chick tissues can transmit this disease to rats and monkeys.

b. Levels of 0.6 *ppb* of tetradoxin produce *ca.* LD<sub>80</sub> effects in guinea pigs, and 0.125 *ppb* are embryotoxic in rats. Yet, the Committee concludes, in the total absence of cited information, that humans cannot be exposed to these

levels. The Committee also appears to ignore the fact that these levels are well below current analytic sensitivity limits of 50 *ppb*, or at best 10 *ppb*. Such analytic procedures are grossly insensitive, compared to the acute toxicological effects of dioxin, which approaches that of the botulinus toxin in biological activity.

c. The Committee does not consider problems of carcinogenicity or mutagenicity due to tetradoxins, and fails to mention that there are no data on these important problems.

d. The Committee does not consider any other of the *ca.* 60 chloro isomers of dioxins which do not appear to have yet been looked for in 2,4,5-T, and does not consider the possibility of their carcinogenic, mutagenic or teratogenic effects.

e. The Committee does not consider possibilities of production of any dioxins from pyrolysis of the 5% trichlorophenol impurities present in current formulations of 2,4,5-T; the 5% impurities are dismissed as toxicologically insignificant.

f. The Committee does not consider problems of chronic inhalation exposure to dioxins or 2,4,5-T.

g. In one section of the report (p. 14) it is stated that current 2,4,5-T formulations contains <1.0 *ppm* of the tetra dioxin; elsewhere (p. 28) the level of dioxin is cited as <0.5 *ppm*.

12. The Committee's analysis of the Vietnam data on possible herbicide effects can only be regarded as poorly comprehensible:

a. The Committee states that "any attempt to relate birth defects or stillbirths to herbicide exposure is predestined to failure".

Such an opinion was considered "extraordinary" by Dr. Matthew Meselson, Chairman of the select AAAS Herbicide Commission, who maintains that properly designed surveys can *possibly* establish such relationships. Also, the Committee viewpoint is not apparently shared by the Department of Defense, who have recently commissioned a National Academy of Sciences Report on this very subject. A Committee member is recently alleged to have confessed that the Committee statement was "an overdramatic and rather poor way of putting it". The dissenting Committee member claims that the report evinces "an unjustified certainty" that the Vietnam data excludes the possibility of teratogenic defects.

b. It is possible that the AAAS report of increased still birth rates in Vietnam could have been an artefact, unrelated to herbicide exposure, as indeed the AAAS Commission carefully points out while recommending the critical need for further study in Vietnam; but, as the Minority Committee Report states: "Factors could just as easily have worked to hide a large still birth rate than to spuriously create one". The Committee appears to ignore this possibility.

c. The Committee appears presumptuous in discounting the implications of the select AAAS Vietnam Report, without detailed substantiation for so doing.

13. The Advisory Committee is totally unresponsive to its charge to discuss alternatives to the use of 2,4,5-T and to assess the economic benefits and penalties attendant on the cancellation or suspension of its registrations. Such data are available in the open literature. Illustrative, is the USDA Agricultural Economic Report No. 199, March 1971, entitled "Restricting the Use of 2,4,5-T; Costs to Domestic Users". This report states that the economic costs to domestic users of banning 2,4,5-T in 1969 would have been only \$52 million, providing all other herbicides could still be used, and \$172 million if other phenoxy herbicides were also restricted.

#### E. CONCLUSIONS

In conclusion, I make the following recommendations:

1. The present restrictions on 2,4,5-T should be maintained until the underlying scientific questions on its experimental toxicity can be properly resolved to the satisfaction of the open and disinterested scientific community. High priority should be accorded to such experiments, particularly to problems of dioxin accumulation in food chains, and to proper investigations of teratogenic dose-response relationships of 2,4,5-T, its commercial formulations and variants, including Silvex, and dioxins.

2. Urgent consideration should be directed to the impropriety of decision-making processes, on issues of critical environmental and public concern, conducted in secrecy and in the absence of formal representation of qualified scientific and legal representatives of public interest and other concerned groups.

3. The statements of Mr. Ruckelshaus that the public-at-large cannot be continually exposed to potential and serious hazards until adequate research has resolved outstanding problems are to be warmly commended. It is recommended that this philosophy be uniformly applied in all pending and future regulatory practice.